Hypothesis: an erythropoietin honeymoon phase exists

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TREAT was a recently concluded, and well-powered and designed, study of anemia treatment in chronic kidney disease (CKD). Unlike most previous studies of ESA treatment in nondialysis CKD, TREAT was a placebo-controlled trial. The placebo group in TREAT provides a unique long-term view of a conservative approach to anemia management in nondialysis CKD. The course of mean Hgb levels in the placebo group ran counter to expectations, increasing over time. We discuss possible reasons for this, including a new hypothesis that there may be an erythropoietin 'honeymoon phase' similar to that observed in diabetes mellitus. We propose investigation of this phenomenon as it could lead to less expensive and safer approaches to treatment of CKD anemia.

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The recent publication of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study[1] marks a landmark moment in our understanding of the anemia of chronic kidney disease (CKD) and its treatment. Despite 20 years of the FDA (Food and Drug Administration)-approved use of erythropoiesis-stimulating agents (ESAs) for anemia treatment in CKD, most published studies on the utility of treatment have been underpowered and, more importantly, have generally lacked a placebo control. The TREAT study was designed as a 4000-patient, double-blinded, randomized, placebo-controlled trial. This rigorous methodology makes it the most important study published to date on anemia treatment in CKD. The reported results are fascinating, and lead to a necessary reconsideration of anemia in CKD and how treatment should be applied. In particular, the course of anemia in the placebo group of TREAT raises fundamental new questions about the natural history of the anemia of CKD. In this commentary, we will propose the hypothesis that as for insulin in type 1 diabetes mellitus (another hormone deficiency state), an erythropoietin honeymoon phase may exist in the anemia of CKD. Regardless of whether this hypothesis is subsequently supported or refuted, the 'natural history' as described by the placebo group in TREAT offers interesting observations with important clinical implications.

The honeymoon phase in type 1 diabetes is a period that occurs after the initial disease presentation, during which the disease seems to temporarily become less severe. A recently proposed definition is, 'a period when the insulin need is 50% or less of the original insulin dose while maintaining good metabolic control.'[2] The remission that occurs during the honeymoon phase is usually partial but could also be complete.[2] In the United States, a honeymoon phase occurs in approximately 42% of patients with newly diagnosed type 1 diabetes mellitus.[3] A honeymoon phase in the anemia of CKD might be operationally defined as a period after the initial dependence of ESA treatment in which dose requirements decline by 50% while hemoglobin (Hgb) is maintained between 10 and 12 g/dl for a period of >3 months.

THE TREAT PLACEBO GROUP

TREAT included participants with type 2 diabetes mellitus, estimated glomerular filtration rate of 20–60 ml/min, and Hgb <11 g/dl. Subjects from 623 sites in 24 countries were

randomized in a 1:1 ratio to treatment with darbepoetin alfa (Aranesp; Amgen, Thousand Oaks, CA) or placebo. Blinded Hgb testing was used to guide darbepoetin dosing to a target Hgb of 13 g/dl. Placebo-treated patients received rescue therapy with darbepoetin if their Hgb levels fell to <9.0 g/dl, and subsequently returning to placebo as soon as their Hgb levels rose to >9.0 g/dl.

The placebo group comprised 2026 patients whose mean duration of follow-up was 29.1 months. This cohort obviously represents a group of impressive size with a significant duration of follow up. Although the placebo group cannot be considered to truly represent the natural history of CKD-related anemia, it does represent a cohort with very conservatively treated anemia. Processes that differed from the natural history included: (1) the use of darbepoetin therapy to 'rescue' if a patient's Hgb fell to <9 g/dl, with immediate termination of treatment as soon as the Hgb was >9 g/dl, (2) the use of both oral and intravenous iron treatment, (3) blood transfusion for severe anemia, and (4) the close observation that occurs with research study participation.

AN ERYTHROPOIETIN 'HONEYMOON' PERIOD?

One of the most fascinating findings of the TREAT study was the Hgb levels observed in the placebo group. The entry criterion of Hgb <11 g/dl resulted in a mean Hgb at baseline in the placebo group of 10.4 g/dl. One might have speculated, *a priori*, that as the CKD of patients progressed over the years of observation, the mean Hgb would decline as well. But, instead of declining, the mean Hgb level rose progressively over time, reaching a mean Hgb of approximately 11.1 g/dl at 48 months. This relative stability or improvement in mean Hgb concentration was unexpected and raises questions about the course of the anemia due to CKD.

Various factors could explain the stability of mean Hgb in the TREAT placebo group. One hypothesis is that the natural history of anemia in CKD may be more complex than previously thought. In classic CKD-related anemia, relative erythropoietin deficiency results in a failure to maintain balance between red cell production and red cell loss to senescence.[4–6] Presumably, once anemia develops, it is a chronic and progressive condition. But this assumption has not been well tested. In fact, we have often observed that many patients, after initiating ESA treatment, gradually require smaller doses with less frequent administration. This raises the question of whether the underlying anemia may have improved, whether these patients still require any ESA therapy, or whether many are initiated on an ESA during a period of decreased responsiveness to their endogenous erythropoietin that subsequently resolves. It is unlikely that many nephrologists test ongoing ESA necessity by a prolonged challenge of withholding treatment. The TREAT placebo results would seem to suggest that at least some patients with mild anemia in CKD may only temporarily require ESA treatment as the severity of their anemia may improve but definitely varies over time.

Erythropoietin deficiency typically develops slowly in CKD.[4–6] The deficiency is relative, with erythropoietin levels appearing normal but lower than expected for the degree of anemia. Radtke *et al.*[7] measured serum erythropoietin levels in 135 subjects with CKD and 59 subjects with normal kidney function. Serum erythropoietin levels were found to be elevated in patients with CKD compared with those with normal kidney function. However, the relationship between serum erythropoietin level and Hgb level varied based on kidney function. Among those with mild CKD, investigators found a normal erythropoietin response to anemia in that lower Hgb levels were associated with higher measures of serum erythropoietin. With more advanced CKD, serum erythropoietin levels were found to be inappropriately low for the degree of anemia present. Among those with a creatinine clearance of <40 ml/min, serum erythropoietin concentration decreased as creatinine clearance declined, indicating a parallel loss of renal excretory function and erythropoietin production capacity. Despite the diminished erythropoietin response with advanced CKD, some degree of feedback response to Hgb remains. In the 6 months before starting dialysis, as anemia worsens, although serum erythropoietin levels are lower than expected, they do increase in reaction.[7] This was confirmed by Walle *et al.*,[8] who found that erythropoietin levels increased after hemorrhage and declined after blood transfusion in dialysis patients. Taken together, these and other[9] studies indicate that in CKD: (1) levels of serum erythropoietin are generally higher than in patients without kidney disease, (2) serum erythropoietin levels increase as Hgb declines in mild-to-moderate CKD, (3) serum erythropoietin levels fail to increase sufficiently for the levels of anemia among patients with creatinine clearance of <40 ml/min, and (4) even with severe CKD, some degree of responsiveness to lower Hgb is retained, although blunted in magnitude. The state of erythropoietin production and responsiveness in CKD suggest that anemia should be fairly mild, or at least relatively easy to treat. In fact, this is exactly what was found in the placebo group of the TREAT study.

One facet of erythropoietin production in CKD that is poorly understood is what happens during an acute illness or episode of increased inflammation. It is possible that an intercurrent illness or other event could cause a transient decline in erythropoietin production and serum concentration. This could result in a transient period of worsening anemia, for weeks or months, before the eventual later development of more severe erythropoietin deficiency, with sustained anemia and when a true chronic need for ESA therapy develops. When the patient recovers from the acute event, Hgb levels would rise, perhaps for an extended period before more intractable erythropoietin deficiency develops. This phenomenon might sound familiar, as it is often observed in another hormone deficiency state, in diabetes mellitus—the so-called 'honeymoon phase.'[10] Given this, it is possible that practically or physiologically a similar 'honeymoon phase' may occur in some or all patients with

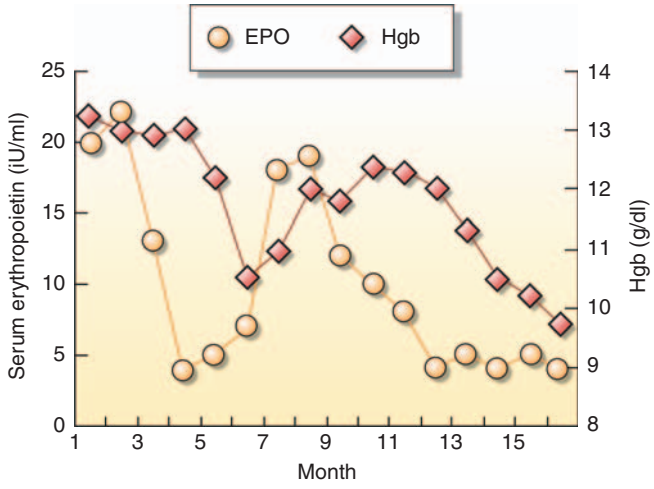

Figure 1 | The stability and increase in mean hemoglobin (Hgb) in the placebo group of the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) study suggest the possibility that a 'honeymoon phase' could exist in some patients with the anemia of chronic kidney disease (CKD). With CKD, serum erythropoietin levels tend to be normal, but lower than expected for patients with reduced Hgb levels. It can be hypothesized that an acute event such as infection could result in a more abrupt, transient, decline in serum erythropoietin levels, followed by worsening of anemia. As the acute event abates, serum erythropoietin levels could temporarily recover to previous levels, and Hgb may improve as well. Eventually, over time, however, as CKD progresses, a more severe deficiency of erythropoietin could develop, resulting in protracted anemia requiring chronic erythropoiesis-stimulating agent (ESA) therapy. The intervening recovery period for serum erythropoietin and Hgb would be analogous to the 'honeymoon phase' sometimes observed in another hormone deficiency state, diabetes mellitus.

CKD-related anemia (Figure 1). This phenomenon might be explained by the recognition of anemia and the initiation of ESAs in two distinct groups of patients: (1) those with a transient hyporesponsiveness because of a recognized or unrecognized physiologic stressor and (2) those with later-stage erythropoietin deficiency. Although the latter group may require continued dosing of ESA, the former may be able to be treated more as the placebo group in TREAT: with conservative temporary interventions. Further analysis of the placebo group will help to better understand the plausibility of this phenomenon.

If an erythropoietin honeymoon phase exists in some or all CKD patients, it raises interesting questions regarding how ESA therapy should be administered. In actual clinical practice, the development of anemia usually leads to initiation of ESA therapy in many patients if Hgb levels declined to <10 or 11 g/dl. Currently, most patients with CKD anemia are probably treated to a target Hgb range of 10–12 g/dl. After the acute illness, when erythropoietin levels rose (the honeymoon phase), Hgb levels could increase in both the presence and absence of ESA therapy. For patients who had ESA dosing initiated, the increase in Hgb might result in reduction in ESA dose or increase in the interval between doses. Many patients may continue on low doses of ESA treatment indefinitely. The question that this hypothesis raises is whether these low doses are necessary. This is speculative, and additional information is required to truly understand how ESA therapy interacts with the natural history of CKD-related anemia. But without knowing the mechanisms, the TREAT study placebo results are clear; that is, conservatively managed CKD anemia can be quite successful. Although this could be explained by informative censoring as follow-up lengthened, the possibility that it could be related to a more complicated physiologic process should be evaluated. Regardless, as we seek to assimilate the results of the recent major anemia trials into practice, this represents an interesting treatment strategy of watchful waiting or brief ESA rescue therapy, which might be an appropriate start to nondialysis CKD anemia treatment.

Beyond a hypothesized erythropoietin honeymoon phase, there are certainly other factors that could explain the TREAT placebo group's Hgb stability/improvement. First, 46% of the placebo group required at least temporary 'rescue' treatment with darbepoetin. It is possible that 'rescue' treatment partially explains the placebo group's Hgb stability. Second, there were more blood transfusions in the placebo (24.5%) compared with the treatment group (14.8%). As transfusion is generally reserved for severe anemia, and as the mean study follow-up was >2 years in most patients (and 4 years in others), the transient effect of transfusion for severe anemia is not likely to explain a rise in Hgb but rather a failure to fall. Third, being in a monitored research study with periodic iron testing, it is likely that placebo patients received more iron treatment than they would have before study entry. Intravenous iron treatment was administered in the placebo group, at some point, in 20.4% of patients (the study publication did not specify the duration or dosage of treatment). Oral iron treatment, although of unclear benefit, was increased from 42.7% at baseline to 68.6% during the study. This somewhat greater use of iron treatment might partially explain the stability in mean Hgb. Fourth, the apparent Hgb rise may reflect a survivor effect, in which participants with the lowest Hgb levels experience a higher mortality rate, and hence as time progresses, the mean Hgb is increased in the surviving group.

In conclusion, a honeymoon phase after ESA initiation may exist in CKD-related anemia similar to that what is observed in diabetes mellitus. Further research on this phenomenon (1) will lead to a greater understanding of the course of CKD anemia, (2) might change the way treatment with ESAs is used, and (3) may lead to a more complete understanding of the relationship between illness and erythropoietin biology. To the extent that an erythropoietin honeymoon phase exists, it would suggest, as found in the TREAT study's placebo group, that watchful waiting and delaying ESA treatment or transient ESA rescue therapy while allowing the patient's Hgb level to gradually rise on its own could be a cost-effective, convenient, and safe approach for many patients.

DISCLOSURE

All the authors declared no competing interests.

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